REMARKS/ARGUMENTS

The claims are not being amended herein. Applicant responds to the Examiner's remarks in the order made.

As noted previously in the prosecution, it is believed that all claims currently pending have priority to 60/137,010. Accordingly, Dale Schenk is the sole inventor of these claims. The other named inventors contributed to claims not now being pursued. The Examiner has not indicated any disagreement with this assessment of priority. Accordingly, applicant intends to file a change of inventorship.

All claims stand rejected as allegedly obvious over Ueda in view of US 6,416,947, US 5,583,112 and US 6,172,122. Ueda is cited regarding using NAC fragments conjugated to KLH to make polyclonal sera in rabbits. The '947 patent is cited regarding use of lipid A or aluminum hydroxide as adjuvants and as teaching that making a vaccine under GMP conditions results in less potency. The '112 patent is cited regarding use of QS21 as an adjuvant. The '122 patent is cited regarding the goals of good manufacturing practice in avoiding adulteration. This rejection is respectfully traversed.

Initially, it is noted that a similar rejection was made and withdrawn earlier in prosecution in which Yoshimoto or Wakabyashi was cited as using alpha synuclein fragments to raise polyclonal sera and a secondary reference Cleland was cited as teaching a stable preparation of QS21 in the context of a HIV vaccine.

The Ueda reference has overlapping authorship with the Yoshimoto and Wakabyashi and describes the same procedure for making polyclonal sera to alpha synuclein fragments. Indeed, the nine amino acid NAC peptide "X1" described in Yoshimoto at p. 9141, second column, 3rd paragraph appears to be the very same peptide as the nine amino acid NAC peptide "X1" described at p. 11282, second column, third paragraph of Ueda. Thus, it appears that Udea is in fact describing preparation of the same polyclonal antibody preparation as Yoshimoto. Like Yoshimoto and Wakabyashi, Udea is silent as to which adjuvant was used. In the case of Yoshimoto and Wakabyashi, it can be conclusively determined that the adjuvant was Freund's adjuvant (complete Freund's adjuvant followed by incomplete Freund's adjuvant) from

cited references as discussed in a previous response. In the case of Ueda, no citations are provided providing further details of antibody production. Nevertheless, because of the overlapping authorship, and the discussion of the same procedure for generating polyclonal antibodies if not the very same preparation of polyclonal antibodies, the skilled person would reasonably infer that Ueda also used Freund's adjuvant as for Yoshimoto and Wakabyashi.

The '697 patent mainly discusses an adjuvant termed a poloxamer. The potency of the adjuvant is compared with Freund's adjuvant, alum, Quil A (of which QS-21 is a component) and a Ribi oil and water formulation. Both the poloxamer and Freund's adjuvant were characterized as "potent adjuvants" inducing "high titered antibody responses" (col. 20, lines 1-8). However, the poloxamer was found to be more immunogenic than alum and Quil A and possibly more immunogenic than Ribi O/W (col. 20, lines 19-22).

Applicant is unable to find any discussion of good manufacturing practice (GMP) in the '697 patent and requests clarification from the Examiner on this point. However, for purposes of responding to the office action only, applicant will assume the Examiner is correct that the art teaches that vaccines made under GMP conditions have reduced potency.

The case of obviousness as understood by applicant is that it would have been obvious to modify Ueda's use of alpha synuclein to generate polyclonal antibodies so that it was performed under GMP conditions and with one of the claimed adjuvants because GMP conditions would lead to greater purity albeit reduced potency and the adjuvant would compensate for the reduced potency. Applicant disagrees with this combination of the references for multiple reasons.

First, it is believed the office action is assuming that Ueda did not use any adjuvant. This assumption is almost certainly incorrect. As discussed above, it is more likely that Udea used complete Freund's adjuvant followed by incomplete Freund's adjuvant as for Yoshimoto and Wakabyashi.

Second, the case of obviousness assumes that laboratory researchers would voluntarily make a polyclonal antibody as a research reagent under GMP conditions. Such assumption is respectfully submitted to be implausible. The considerations facing drug manufacturers, to whom GMP regulations are directed, and laboratory researchers are entirely

different. Drug manufacturers make large quantities of a drug for a therapeutic use. Laboratory researchers make relatively small quantities of a polyclonal antibody for research use; moreover, the animal used in the experiment is usually sacrificed at the end of the experiment. The precautions and procedures imposed on manufacturers of drugs to ensure purity and safety of patients would appear an unnecessary and onerous burden to a laboratory researcher and would not be self-imposed. No evidence has been provided that GMP conditions have ever been used in laboratory research.

Third, the case of obviousness assumes that alum or lipid A would be administered to compensate for a loss of potency caused by manufacture under GMP conditions. However, the '697 patent does not provide any evidence that alum and lipid A are more potent that its polyoxamer or Freund's adjuvant and in fact suggests the reverse is the case. Accordingly, one would not have been motivated to replace Freund's adjuvant with alum or lipid A due to concerns regarding inadequate potency of Freund's adjuvant.

The rationale for combining alpha synuclein or fragments with an adjuvant suitable for human administration arises from the unexpected recognition in the present application that immunization with alpha synuclein to generate antibodies has a useful pharmacological activity. Although it is recognized that reason for combining references need not be the same as that of applicant, the reason cannot be based on hindsight. "A factfinder should be aware ....of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning," *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1397 (2007).

Here, as in the previous obviousness rejection, it is respectfully submitted there are a number of indicia that the combination of references rests on hindsight rather than being a realistic assessment of the mindset of the artisan at the relevant time. The case of obviousness simply assumes that Ueda did not use an adjuvant, whereas closer examination of the circumstances indicates it is more likely that he used complete and incomplete Freund's adjuvant as did other references with overlapping authorship making polyclonal sera to alpha synuclein in rabbits. The case of obviousness assumes a laboratory researcher would self-impose GMP conditions without any evidence that such conditions have ever been employed by any laboratory

worker. The case of obviousness assumes that the skilled person would use alum or lipid A to compensate for a loss of potency from using GMP conditions, when it is likely that Udea was already using a more potent adjuvant (i.e., Freund's adjuvant).

For these reasons, withdrawal of the rejection is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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